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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,250	11/26/2003	Thomas M. DiMauro	3518.1024-000	6059

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EXAMINER	
MAEWALL, SNIGDHA	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
10/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,250	DIMAURO ET AL.	
	Examiner	Art Unit	
	Snigdha Maewall	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-10,21-25,27-30,60,70,89,91 and 92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-10,21-25,27-30,60,70,89,91 and 92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/22/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt of Applicants' arguments /remarks and IDS filed on 07/22/10 is acknowledged.

Claims **6-7, 26 and 57-58** have been canceled. Claims **11-20, 31-56, 59, 61-69, 71-88** and **90** have been withdrawn.

Claim 60 has been amended.

Accordingly, claims **1-5, 8-10, 21-25, 27-30, 60, 70, 89 and 91-92** are being examined on the merits herein.

The following are new rejections based on further search, according this office action is made non final. The previous rejections have been withdrawn in light of applicant's arguments.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 1 recites the limitation "into the bone" administration and also recites the limitation that bone is intact in claim 2. It is unclear to the examiner if the administration of bone forming agent and TNF antagonist is to all the bone of body or to any specific bone. In osteoporosis, every bone of body is considered osteoporotic, does applicant mean administering the drug to every possible bone in body. The term is confusing and thus indefinite especially in light of the limitation "intact" bone. Since all the bones are intact in body, the administration to which part/specific bone of body is not defined and thus it is unclear (considering the fact that there are around 208 bones in human body). The claims also do not define mode of administration in claim 1, it is not clear whether applicant intends to claim injection, implant or depot.... Absent indication of patient population and the duration of treatment and the effective amount, it is not clear how the treatment is possible for all the intact bones of a human body.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radomsky (US 5,942,499) in combination

with Allali et al. (Ann Rheum Dis 2003; 62: 347-349), Bertolini et al. (Nature Vol. 319 6 February 1986) Brandt et al., (Arthritis and Rheumatism vol. 43. no. 6, June 2000, 1346-1352) or vice versa.

Radomsky teaches administration of growth factors to bone. Radomsky teaches a bone growth-promoting composition comprising growth factors such as fibroblast growth factor and platelet-derived growth factor and their methods of use (column 1, lines 19, 35-36, and 61). The invention can be used in various sites of desired bone growth including vertebral compression fractures and in pathological bone defects associated with osteoporosis (column 2, lines 50 and 55-58). The invention describes an **injectable mixture of growth factor for intraosseous, or within bone, administration** (column 12, lines 5-12).

The reference does not teach administration of anti-resorptive agent, such as remicade/infliximab which is a highly specific cytokine antagonist.

Allali et al. teaches increase in bone mineral density of patients with spondyloarthropathy treated with TNF alfa, antagonist title. The reference teaches that **osteoporosis** is commonly associated with ankylosing spondylitis. The cytokine has been shown to mediate the increase of bone resorption in systemic osteoporosis related to estrogen deficiency, see page 347, columns 1 and 2. Infliximab is a human/mouse neutralizing chimeric monoclonal antibody of IgGIk isotype with specificity and high affinity for TNF alfa. It has been successfully used in treatment of spondyloarthritis and rheumatoid arthritis; see page 347, column 2, and first paragraph. Under references section, Kimble et al. has been disclosed to teach functional block of TNF prevents

bone loss, Ammann et al. teaches bone loss caused by estrogen deficiency to be treated with TNF antagonist, **Bertolini et al**. teaches stimulation of bone resorption and inhibition of bone formation by TNF, **Brandt et al.** teach treatment of ankylosing spondylitis by TNF antagonist infliximab (see the entire references).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the antiresorptive agent while treating osteoporotic bone such as infliximab motivated by the teachings of Allali et al. One of ordinary skill would have combined the treatment of osteoporotic bone by using antiresorptive agent such as infliximab as taught by Allali et al. with the Randomsky's teachings because Randomsky teaches utilizing bone growth factors in treating pathological bone defects associated with osteoporosis by local intraosseous administration and Allali teaches **osteoporosis** is commonly associated with ankylosing spondylitis. Since osteoporosis is commonly associated with ankylosing spondylitis , one of ordinary skill would envisage treatment of osteoporosis also by utilizing infliximab, which is an antibody that inhibits TNF alfa. Since osteoporosis is known in the art to have uncoupled bone resorption, one would expect treatment of uncoupled resorption of bone by infliximab treatment. Since Radomsky teaches addition of mixtures, one would have been motivated to add remicade/infliximab in addition to other bone forming agents and would have had reasonable expectation of success in obtaining an improved and better combination of treating osteoporosis or bone related treatment. One of skill in the art would have recognized that the results of the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention

was made, as demonstrated by the teachings of the Radomsky and Allali and Bertolini and Brandt's publication. Since Radomsky teaches administration the bone forming agent to bone, it would have been obvious to one of ordinary to administer the bone forming agent and antiresorptive agent such as infliximab to hip or any vertebral part of body. By utilizing infliximab, one of ordinary skill would have expected treatment of osteoporotic bone in a patient by administering infliximab in an uncoupled resorbing bone because Allali and Brandt teaches that infliximab has been shown to mediate the increase of bone resorption in osteoporosis related deficiency.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. Claims 1-3, 5, 8-10, 21-23, 25, 27-30, 70, 89 and 91-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radomsky (US 5,942,499) in combination with Allali et al. (Ann Rheum Dis 2003; 62: 347-349) , (Kitazawa et al. J. Clin. Invest. Volume 94, December 1994, 2397-2406) and Brandt et al. (Arthritis and Rheumatism vol. 43. no. 6, June 2000, 1346-1352) or vice versa.

Radomsky teaches administration of growth factors to bone. Radomsky teaches a bone growth-promoting composition comprising growth factors such as fibroblast growth factor and platelet-derived growth factor and their methods of use (column 1,

lines 19, 35-36, and 61). The invention can be used in various sites of desired bone growth including vertebral compression fractures and in pathological bone defects associated with osteoporosis (column 2, lines 50 and 55-58). The invention describes an **injectable mixture of growth factor for intraosseous, or within bone, administration** (column 12, lines 5-12).

The reference does not teach administration of anti-resorptive agent, such as remicade/infliximab which is a highly specific cytokine antagonist.

Allali et al. teaches increase in bone mineral density of patients with spondyloarthropathy treated with TNF alfa, antagonist title. The reference teaches that **osteoporosis** is commonly associated with ankylosing spondylitis. The cytokine has been shown to mediate the increase of bone resorption in systemic osteoporosis related to estrogen deficiency, see page 347, columns 1 and 2. Infliximab is a human/mouse neutralizing chimeric monoclonal antibody of IgGIk isotype with specificity and high affinity for TNF alfa. It has been successfully used in treatment of spondyloarthritis and rheumatoid arthritis; see page 347, column 2, and first paragraph. Under references section, Kimble et al. has been disclosed to teach functional block of TNF prevents bone loss, Ammann et al. teaches bone loss caused by estrogen deficiency to be treated with TNF antagonist, **Kitazawa et al.** teaches Tumor necrosis factor binding protein decrease osteoclast formation and bone resorption, **Brandt et al.** teach treatment of ankylosing spondylitis by TNF antagonist infliximab (see the entire references).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have utilized the antiresorptive agent while treating osteoporotic bone such as infliximab motivated by the teachings of Allali et al. One of ordinary skill would have combined the treatment of osteoporotic bone by using antiresorptive agent such as infliximab as taught by Allali et al. with the Randomsky's teachings because Randomsky teaches utilizing bone growth factors in treating pathological bone defects associated with osteoporosis by local intraosseous administration and Allali teaches **osteoporosis** is commonly associated with ankylosing spondylitis. Since osteoporosis is commonly associated with ankylosing spondylitis , one of ordinary skill would envisage treatment of osteoporosis also by utilizing infliximab, which is an antibody that inhibits TNF alfa. Since osteoporosis is known in the art to have uncoupled bone resorption, one would expect treatment of uncoupled resorption of bone by infliximab treatment. Since Radomsky teaches addition of mixtures, one would have been motivated to add remicade/infliximab in addition to other bone forming agents and would have had reasonable expectation of success in obtaining an improved and better combination of treating osteoporosis or bone related treatment. Since Kitazawa et al. teaches Tumor necrosis factor binding protein decrease osteoclast formation and bone resorption, one of skill in the art would have recognized that the results of the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made, as demonstrated by the teachings of the Radomsky, Allali and Kitazawa et al and Brandt's publication, that is treatment of uncoupled resorption in osteoporotic bone. Since Radomsky teaches administration of

the bone forming agent to bone, it would have been obvious to one of ordinary to administer the bone forming agent and antiresorptive agent such as infliximab to hip or any vertebral part of body. By utilizing infliximab, one of ordinary skill would have expected treatment of osteoporotic bone in a patient by administering infliximab in an uncoupled resorbing bone because Allali, Kitazawa and Brandt teach that infliximab has been shown to mediate the increase of bone resorption in osteoporosis related deficiency.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claims 4 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radomsky (US 5,942,499) in combination with Allali et al. (Ann Rheum Dis 2003; 62: 347-349), Bertolini et al. (Nature Vol. 319 6 February 1986) Brandt et al., (Arthritis and Rheumatism vol. 43. no. 6, June 2000, 1346-1352) as discussed above and further in view of Boyle et al. (US 2003/0207827).

The references discussed above do not teach patient as post menopausal.

Boyle et al. teach methods to treat bone diseases such as osteoporosis comprising osteoprotegrin, which is a polypeptide that plays a role in promoting bone accumulation (page 1, paragraphs [0001] and [0006]). Boyle et al. further teach

treatment of osteoporosis in postmenopausal women and a direct relationship between osteoporosis and incidence of hip and neck fractures (page 9, paragraph [0095]). Osteoprotegrin acts as a receptor of the TNF family and prevents receptor-ligand interaction (page 4, paragraph [0043]). Osteoprotegrin also blocks interleukin (IL)1-α and IL1-β produced hypercalcemia (page 40, paragraph [0344]). Boyle et al. also teaches that **estrogen is a known anti-resorptive agent (page 41, paragraph [0355]).**

It would have been obvious to one of ordinary skill in the art at the time of instant invention to utilize the bone forming agent and remicade, an anti resorptive agent to post menopausal women as a patient motivated by the teachings of Boyle et al. teaching the administration of antiresoptive agents for treatment of osteoporosis in post menopausal women.

8. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Radomsky (US 5,942,499) in combination with Allali et al. (Ann Rheum Dis 2003; 62: 347-349), Bertolini et al. (Nature Vol. 319 6 February 1986) Brandt et al., (Arthritis and Rheumatism vol. 43. no. 6, June 2000, 1346-1352) as discussed above and further in view of Trieu et al. (US PG pub. 2002/0026244).

The references discussed above do not teach implants.

Trieu teaches methods of implanting nucleus pulposus implants (page 1, paragraph [0007]). The method involves removal of the natural nucleus pulposus of the intravertebral disc and implantation of the nucleus pulposus of the invention (page 10,

paragraph [0109]). The nucleus pulposus implant of the invention may contain pharmacological agents used to treat osteoporosis including a bone morphogenetic protein, growth factors such as fibroblast growth factor and platelet-derived growth factor, and steroids (page 9, paragraphs [0101] and [0104]). The device of Trieu is placed adjacent to unfractured bones (page 9, paragraphs [0104]). Since the nucleus pulposus implant of the invention may contain pharmacological agents used to treat osteoporosis including a bone morphogenetic protein (see page 9, paragraph [0101]), it would be obvious that the device can be used to treat fractured bones such as a hip bone. Thus Trieu teaches local administration in between bones.

It would have been obvious to the one of ordinary skilled in the art at the time the invention was made to incorporate highly specific cytokine antagonist such as remicade as taught by primary references to the teachings of Trieu since the reference teaches advantage of the same in treating osteoporosis with bone morphogenetic protein etc. One skilled in the art would have been motivated to administer into the bone the formulation comprising the bone forming agent and remicade because Trieu et al. successfully teach local administration of implants/drug in between bones in order to treat osteoporosis.

CITED AS INTEREST

Weitzmann et al., The Journal of clinical investigation, Dec. 2002, vol 10, 1643-1650.

(Bone remodeling in osteoporosis (Clinical Rhematology 1989, 8 suppl. N 2), Breban et al. Efficacy of infliximab Rhematology, and 2002, 41; 1280-85.

All of the above references have been cited to show that infliximab helps in decreasing bone resorption and uncoupled bone resorption during osteoporosis.

Response to Arguments

9. Applicant's arguments with respect to claims **1-5, 8-10, 21-25, 27-30, 60, 70, 89 and 91-92** have been considered but are moot in view of the new ground(s) of rejection.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/

Examiner, Art Unit 1612

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612